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Perspective

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Endocrine effects of heat exposure and relevance to climate change

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Abstract

Climate change is increasing both seasonal temperatures and the frequency and severity of heat extremes. As the endocrine system facilitates physiological adaptations to temperature changes, diseases with an endocrinological basis have the potential to affect thermoregulation and increase the risk of heat injury. The effect of climate change and associated high temperature exposure on endocrine axis development and function, and on the prevalence and severity of diseases associated with hormone deficiency or excess, is unclear. This Perspective summarizes current knowledge relating to the hormonal effects of heat exposure in species ranging from rodents to humans. We also describe the potential effect of high temperature exposures on patients with endocrine diseases. Finally, we highlight the need for more basic science, clinical and epidemiological research into the effects of heat on endocrine function and health; this research could enable the development of interventions for people most at risk, in the context of rising environmental temperatures.

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Introduction

Global mean surface temperatures are increasing by 0.2 °C per decade owing to climate change[1]. Consequently, most countries are experiencing a rise in daily and seasonal temperatures together with an increase in the frequency, length and intensity of heatwaves (Supplementary Box 1 lists key glossary terms for this Perspective)[1,2]. Hormones influence a variety of physiological responses to temperature changes, ranging from sex determination in reptiles to brown adipose tissue (BAT) thermogenesis in mammals[3,4]. Endocrine diseases have the potential to impair physiological adaptations to high temperatures, which could lead to an increased risk of heat injury or heat-related health effects in patients[5]. However, the effects of heat exposure on endocrine function, disease progression and population health are unclear. A number of studies addressing this topic have investigated the effects of acute heat exposure in non-human animal models or healthy human volunteers. The relevance of such studies to high-risk populations exposed to long-term changes in ambient temperature (Supplementary Box 1) as a consequence of climate change is unclear.

This Perspective describes available evidence relating to the hormonal consequences of heat exposure, with a focus on key stages of the life course and potential effects on patients with endocrine diseases. Furthermore, we emphasize the need for more research, education and health-care provision relating to the effects of climate warming on endocrine health.

Endocrine adaptations to heat

Humans have a core temperature of ~37 °C, mainly achieved through metabolic processes that generate heat. The thermoneutral zone is the range of ambient temperatures at which the body can maintain this core temperature solely through dry (non-sweating) heat loss[6]. Physiological adaptation to heat involves activation of thermoreceptors, mainly in the skin, muscle, viscera and brain, which relay sensory inputs to the preoptic area (POA) of the anterior hypothalamus[7,8]. In rodents, the POA triggers autonomic responses that suppress BAT thermogenesis and promote heat loss by stimulating cutaneous vasodilation to restore thermoneutrality[4,7,8]. In humans, POA activation is associated with autonomic responses that induce sweating in response to heat[9].

Abnormalities of thermoregulation (such as ineffective heat dissipation) can cause heat stress (Supplementary Box 1) which, if sustained or excessive, increases core temperature. An excessive rise in core temperature can cause heat exhaustion or life-threatening heat stroke, or have other health effects such as exacerbations of pre-existing chronic cardiac, renal or metabolic diseases[2,10]. Physical exertion and exercise can also cause heat stress, which arises when metabolic heat from muscle activity exceeds the capacity for heat dissipation[11]. The ability to cope with exertional heat stress is influenced by the capacity of the cardiovascular system to dissipate heat through increased skin blood flow, whilst maintaining adequate tissue perfusion to support metabolic demands during exercise[11]. Sweating is the primary heat-loss mechanism occurring during exercise and can result in high rates of fluid loss. Inadequate fluid replacement can decrease plasma volume, which further exacerbates exertional heat stress and causes cardiovascular strain[11].

The role of the endocrine system in facilitating adaptation to heat during rest and exercise is not fully elucidated. Studies in many species have demonstrated that acute and chronic heat exposure affects numerous hormones (Table 1). Hormones with possible roles in adapting to heat include cortisol, thyroid hormones, arginine vasopressin (AVP), prolactin, growth hormone (GH), insulin and adipokines (Fig. 1). Their roles are described in the following sections.

Heat induces a stress hormone response

Exposure to heat induces a stress response characterized by activation of the autonomic nervous system and hypothalamic–pituitary–adrenal axis, which in healthy humans acutely increases noradrenaline and cortisol secretion[12–14]. In plasma, cortisol is mainly bound to corticosteroid binding globulin (CBG) and the concentration of cortisol is a sensitive heat stress marker, with values correlating with acute elevations in core temperature and body heat storage in healthy humans[12]. A rise in core temperature within the clinically relevant range of 35–42 °C can also cause plasma concentrations of free cortisol to increase due to release of cortisol from CBG[15]. Long-term heat exposure in rats (32 °C for 7 days) additionally led to pituitary and adrenal gland enlargement in association with increased serum concentrations of adrenocorticotropic hormone (ACTH) and cortisol compared with rats at 24 °C[16].

The influence of cortisol and catecholamines on thermoregulation is unclear. In rabbits and rats, these hormones might induce physiological adaptation to heat by acting directly on the POA[17,18] (Fig. 1). Other hormones involved in the stress response include AVP, prolactin and GH (described in subsequent sections).

Suppression of thyroid axis activity might decrease thermogenesis and increase heat loss

Thyroid hormones regulate metabolism and their secretion is influenced by changes in ambient temperature[19]. Indeed, direct cooling of the POA in rats is reported to increase thyroid-stimulating hormone (TSH) secretion[20]. Thyroid hormones increase core temperature by promoting obligatory thermogenesis through effects on cell metabolism and mitochondrial activity, which in turn elevate basal metabolic rate[21]. When this process is insufficient to maintain core temperature, thyroid hormones will stimulate adaptive thermogenesis (mainly mediated by BAT in small mammals) and decrease blood flow-mediated heat dissipation[21]. Heat stress can suppress plasma concentrations of TSH, tetraiodothyronine (T_4) and triiodothyronine (T_3), as shown in cattle exposed to daily temperatures of 32–40 °C compared with cattle maintained at 19 °C[22]. Suppression of the thyroid axis also occurs in humans: exertional heat stroke (Supplementary Box 1) in military recruits was associated with a decrease in serum levels of T_3, a reciprocal increase in reverse T_3 and inappropriately normal serum concentrations of TSH[23]. These findings indicate that heat injury might have caused non-thyroidal illness syndrome and impaired peripheral conversion of T_4 to T_3. The low T_3 state could aid thermoregulation by decreasing metabolic heat generation; hence, exogenous T_3 administration to chickens shortens their survival during heat exposure[24].

Heat also promotes the release of T_4 from thyroxine binding globulin (TBG), which is probably beneficial for increasing metabolism in response to fevers induced by infection and inflammation[25]. However, this response might be detrimental to individuals living in environments with high temperatures. Intriguingly, two missense TBG gene variants (p.Ala191Thr and p.Leu283Phe), which are co-expressed in aboriginal Australian individuals, are reported to confer thermal protection by reducing the release of T_4 in response to heat whilst maintaining TBG storage and carrier functions[25].

AVP and aldosterone regulate water balance in response to heat

In individuals with adequate fluid and electrolyte intake, circulating plasma volume and total body water increase after heat acclimation or acclimatization[26] (Supplementary Box 1). These adaptations support thermoregulation by increasing the capacity for heat loss. However,

Table 1 | Reported effects of heat exposure on hormone secretion or expression

Endocrine axis or pathway	Type of exposure[a]	Exposure conditions	Effect on hormone[b]	Human participants or animal model[c]	Ref.
Stress hormone response					
CRH	Acute	40 °C for 6 h	↑	Chicks	114
ACTH	Chronic	32 °C for 8 h daily over 7 days	↑	Rats	16
Cortisol	Acute (climatic chamber)	43–55 °C for ≤3 h with vapour pressure in the range 15–34 Torr	↑	Humans	12
	Chronic	32 °C for 8 h daily over 7 days	↑	Rats	16
Adrenaline	Acute (water bath)	Lower body warming, 44 °C for ~60 min	↔	Humans	35
	Acute, exercise heat stress	Cycle ergometer for ~45 min at 19–21 °C and 35–45% relative humidity with or without excess clothing	↔	Humans	13
Noradrenaline	Acute (water bath)	Lower body warming, 44 °C for ~60 min	↑	Humans	35
	Acute, exercise heat stress	Cycle ergometer for ~45 min at 19–21 °C and 35–45% relative humidity with or without excess clothing	↑	Humans	13
Water balance					
AVP	Acute (water bath)	Lower body warming, 41 °C for 120 min	↑	Humans	28
	Acute	48 °C for ~120 min	↑	Sheep	115
Aldosterone	Acute (sauna)	85–90 °C for 20 min	↑	Humans	27
Growth hormone					
GHRH	Acute (sauna)	72 °C for 15 min	↑	Humans	37
Growth hormone	Acute (sauna)	72 °C for 15 min	↑	Humans	37
	Acute, exercise heat stress	Treadmill walking until volitional exhaustion at 42 °C and 18% relative humidity	↑	Humans	40
Thyroid					
TSH	Acute, exertional heat stroke	Reported in military recruits	↔	Humans	23
	Chronic (climatic chamber)	Cyclical daily temperatures of 32–40 °C at 20% humidity for 9 days	↓	Steers	22
T_4	Acute, exertional heat stroke	Reported in military recruits	↓	Humans	23
	Chronic (climatic chamber)	Cyclical daily temperatures of 32–40 °C at 20% humidity for 9 days	↓	Steers	22
T_3	Acute, exertional heat stroke	Reported in military recruits	↓	Humans	23
	Chronic (climatic chamber)	Cyclical daily temperatures of 32–40 °C at 20% humidity for 9 days	↓	Steers	22
Hypothalamic–pituitary–gonadal					
Kisspeptin	Chronic, seasonal	Hormonal values in summer (~29–33 °C) compared with spring (18–21 °C)	↓[d]	Pigs	65
GnRH	Chronic, seasonal		↓	Pigs	65
LH	Chronic, seasonal		↓	Pigs	65
FSH	Chronic, seasonal		↓	Pigs	65
Oestradiol	Chronic, seasonal		↓	Pigs	65
	Chronic (climatic chamber)	38 °C for 120 min daily for 2 weeks in climatic chamber with 45–60% humidity	↓	Rats	68
Testosterone	Acute, exertional heat stroke	Treadmill exercise at 36 °C in climatic chamber with ~50% relative humidity	↓	Rats	72
	Chronic	Daily heat exposure (34.5 °C for 8 h, 31 °C for 16 h) for 14 days	↓	Boars	71
Pregnancy and lactation					
Progesterone	Acute (water bath)	Lower body warming, 44 °C for ~60 min	↑	Humans	35
	Chronic (climatic chamber)	38 °C for 120 min daily for 2 weeks in climatic chamber with 45–60% humidity	↓	Rats	68
Prolactin	Acute (water bath)	Lower body warming, 44 °C for ~60 min	↑	Humans	35
	Acute (sauna)	80–85 °C for 20 min	↑	Humans	36
	Chronic	Heat stress for 46 days	↑	Cows	80
Oxytocin	Acute	48 °C for ~120 min	↑	Sheep	115

Table 1 (continued) | Reported effects of heat exposure on hormone secretion or expression

Endocrine axis or pathway	Type of exposure[a]	Exposure conditions	Effect on hormone[b]	Human participants or animal model[c]	Ref.
Pancreas and gut					
Insulin	Chronic (climatic facility)	30 °C for 27 days with ~60% relative humidity	↓	Cows	116
	Chronic (climatic chamber)	35 °C for 5 days	↑	Mice	48
Ghrelin	Acute (climatic chamber)	30 °C for 5.5 h	↔	Humans	57
Peptide YY	Acute (climatic chamber)		↔	Humans	57
Glucagon-like peptide 1	Acute (climatic chamber)		↔	Humans	57
Adipose tissue					
Leptin	Acute, exercise-heat stress	Military personnel, 2-h bouts of physical activities at ~30 °C in climatic chamber with ~31% relative humidity	↑	Humans	55
	Chronic (climatic chamber)	35 °C for 5 days	↑	Mice	48
Adiponectin	Chronic (climatic chamber)	35 °C for 5 days	↑	Mice	48

ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; T_3, triiodothyronine; T_4, tetraiodothyronine; TSH, thyroid-stimulating hormone. [a]Acute refers to sustained or intermittent heat exposure lasting <24 h, and chronic refers to sustained or intermittent heat exposure lasting >24 h. [b]↑, increased; ↓, decreased; ↔, no effect. [c]Reported thermoneutral zones: chicks 29–30 °C[117], mice 29–31 °C[111], rats 29–31 °C[118], dairy cows 0.5–20 °C[119], pigs <18–27 °C[120], sheep 12–27 °C[121], clothed humans 20–22 °C[111]. [d]Decreased hypothalamic expression of kisspeptin.

older adults, patients with chronic diseases and people working in hot environments are often dehydrated and might therefore have limited ability to dissipate heat by increased blood flow or sweating.

Regulation of water balance in response to heat is probably mediated by increased secretion of AVP and aldosterone, which decrease water and sodium excretion, respectively[26] (Fig. 1). In humans, activation of the renin–angiotensin–aldosterone axis occurs within minutes of acute heat stress, as shown in healthy young men exposed to sauna heat (85–90 °C), and this effect might be mediated by increased circulating catecholamines or decreased renal blood flow, both of which increase renin secretion[27] (Fig. 1). AVP might be released as part of the stress response to heat exposure and in humans, its secretion is sensitive to changes in core temperature. A small (≤1 °C) elevation in core temperature potentiates AVP secretion and increases thirst and water intake following hypertonic saline infusion[28]. Heat-induced AVP secretion might also contribute to exercise-associated hyponatraemia in endurance athletes[29].

Studies conducted in rats suggest a thermoregulatory role for AVP: intravenous AVP injection acutely decreased body temperature, whereas a vasopressin V1 receptor antagonist increased body temperature[30]. AVP functions as a neurotransmitter acting on the rat POA, probably via the vasopressin V1a receptor, to excite warm-sensitive neurons that inhibit BAT thermogenesis and promote heat loss (Fig. 1), whilst inhibiting cold-sensitive neurons that promote thermogenesis and heat retention[31].

Prolactin and GH secretion might promote heat loss via sweating

Prolactin and GH are homologous peptides that exert hormonal and cytokine effects[32]. Prolactin facilitates maternal adaptation to pregnancy and stimulates lactation postnatally, whilst GH promotes linear growth in childhood and might also increase cellular senescence in adulthood[33,34]. In sauna and warm water immersion studies in healthy human volunteers, exposure to temperatures in the range 44–85 °C acutely increased plasma concentrations of prolactin, whereas increases in plasma levels of GH occurred in younger but not older men[35–37]. Increases in prolactin and GH might form part of the stress response to heat exposure. Indeed, prolactin acts directly on the hypothalamus, and pituitary and adrenal glands, and stimulates the secretion of corticotropin-releasing hormone, ACTH and cortisol[38,39]. In addition, these hormones might have thermoregulatory roles.

In an exercise heat stress study involving healthy young men, serum concentrations of GH were positively correlated with whole-body sweat production, highlighting that GH and/or its downstream mediator, insulin-like growth factor 1, might act on sweat glands to promote evaporative heat loss[40] (Fig. 1). In keeping with GH having a thermoregulatory role, adult patients with GH deficiency have a decreased density of acetylcholinesterase-positive and vasoactive intestinal peptide-positive nerves supplying sweat glands, which significantly increase following recombinant human GH treatment[41]. Prolactin might also promote sweating (Fig. 1): in healthy young men, a dopamine receptor agonist (which inhibits prolactin secretion) considerably decreased sweating and plasma concentrations of prolactin during an exercise heat stress study[42]. Furthermore, dairy cattle harbouring a germline *PRL* mutation (p.Cys221Gly) had decreased sweating associated with higher rectal temperatures and a heat stress response characterized by increases in respiration rate[43].

Insulin sensitivity might increase or decrease in response to heat

Insulin regulates postprandial tissue uptake, storage and metabolism of glucose, lipids and amino acids[44]. Heat exposure might influence the responsiveness of target tissues to insulin. However, the evidence is conflicting. In aged rats, acute heat exposure that raised core temperature to 41 °C for 20 min increased insulin-stimulated glucose uptake in skeletal muscle, which is consistent with increased insulin sensitivity[45]. The effect was associated with induction of heat shock protein expression that might enhance insulin signalling and protect against insulin resistance by maintaining mitochondrial function and decreasing reactive oxygen species[46,47]. Increased insulin sensitivity leading to utilization of glucose as an energy substrate might help mammals adapt to heat exposure, as the conversion of glucose to ATP is associated with less metabolic heat generation compared with fatty acid oxidation[48]. However, a study involving men with overweight showed no effect of heat exposure (~34 °C for 10 days) on insulin sensitivity as assessed

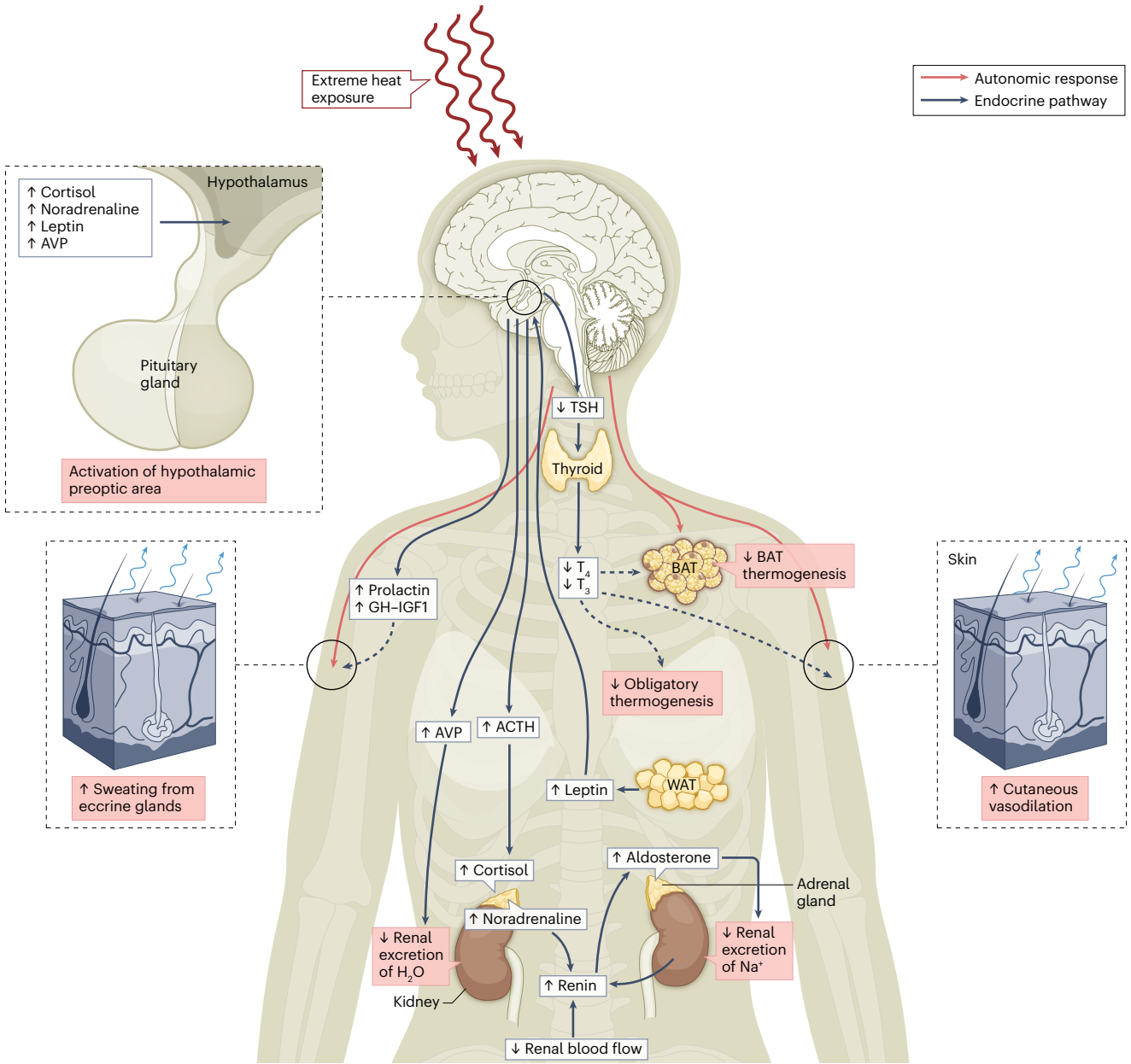

Fig. 1 | Possible involvement of hormones in thermoregulatory adaptation to heat. Changes in temperature affect a range of endocrine systems. These include the hypothalamic–pituitary–adrenal axis and autonomic nervous system (which are involved in the stress response and produce hormones such as cortisol, arginine vasopressin (AVP), prolactin, growth hormone (GH) and noradrenaline); the thyroid axis (which involves hormones such as thyroid stimulating hormone (TSH), tetraiodothyronine (T_4) and triiodothyronine (T_3)); the renin–angiotensin–aldosterone axis (which involves the kidneys, lungs and adrenal glands, and regulates sodium and water balance); and white adipose tissue (WAT; which produces hormones such as leptin that affect appetite and food intake). Heat-induced secretion of hormones such as cortisol, noradrenaline, leptin and AVP might influence the central thermoregulatory network by acting on the hypothalamic preoptic area (POA)[12,13,28,48]. The POA activates autonomic responses (red arrows) that lower core temperature by decreasing brown adipose tissue (BAT) thermogenesis and by promoting heat loss via sweating and increased cutaneous blood flow[7,8]. Heat-induced hormonal changes also affect peripheral thermoregulatory processes. Suppression of the thyroid axis might decrease BAT thermogenesis and obligatory thermogenesis and increase cutaneous blood flow[21,23]. Increased pituitary secretion of GH, which induces secretion of insulin-like growth factor 1 (IGF1), and pituitary secretion of prolactin might increase sweating from eccrine glands[41,43]. Increased AVP secretion decreases renal excretion of H_2O, and heat-induced noradrenaline secretion and decreased renal blood flow leads to activation of the renin–angiotensin–aldosterone system, which results in decreased renal excretion of Na^+ and H_2O[27,28]. Possible hormone actions in response to heat exposure are represented by dashed arrows. ACTH, adrenocorticotropic hormone.

by hyperinsulinaemic–euglycaemic clamp, although fasting plasma concentrations of glucose and insulin were decreased[49].

Increased ambient temperatures have also been associated with insulin resistance in humans. This association was evidenced by the findings of a population-based study in which insulin resistance as defined by HOMA was positively correlated with mean annual temperature, with the association persisting after adjusting for physical activity[50]. Heat-induced insulin resistance might be caused by dehydration, which impairs insulin signalling[5,51], or by decreased BAT activity, which increases fatty acid flux to metabolically active tissues such as skeletal muscle, thereby decreasing insulin-mediated glucose uptake by these tissues[52].

Heat affects adipose tissue and promotes adipokine secretion

Adipose tissue is involved in energy storage and release, thermal insulation and hormone secretion[53]. Heat exposure affects BAT and white adipose tissue (WAT). In rodents, BAT rapidly becomes deactivated following an increase in ambient temperature, thereby reducing excess heat generated by thermogenesis[8]. In mice, heat also affects WAT and activates heat shock factor 1, which triggers WAT browning to beige adipose tissue[54]. This process might have anti-obesogenic effects, and local hyperthermia administered to mouse inguinal WAT over 10 weeks reduced adipose tissue mass and body weight[54]. Reduction of total body WAT might promote heat adaptation by reducing insulation and enhancing heat dissipation.

In addition, exposure to a temperature of 35 °C for 5 days in mice increased adipose tissue expression of adiponectin and leptin, hormones that sensitize peripheral tissues to insulin and promote insulin-mediated glucose uptake[48]. In military recruits exercising under hot conditions at 30 °C, plasma concentrations of leptin were also increased compared with those exercising in temperate (21 °C) or cold (−10 °C) conditions[55]. Heat-induced leptin secretion, in addition to increasing insulin sensitivity, might decrease metabolic heat production by acting centrally to reduce appetite and food intake and suppress BAT thermogenesis[56] (Fig. 1). This mechanism could explain why activation of leptin receptor-expressing POA warm-sensitive neurons in mice decreased core temperature in association with decreases in energy expenditure and food intake[56]. However, increased plasma concentrations of leptin in humans exercising in heat were not associated with changes in appetite or dietary intake[55]. In addition, gut hormones do not mediate heat-related appetite suppression[57]. In a study involving healthy men at rest, exposure to a temperature of 30 °C for 5.5 h significantly decreased ad libitum energy intake without altering the plasma concentrations of acylated ghrelin (an orexigenic hormone) or peptide tyrosine-tyrosine and glucagon-like peptide 1 (anti-orexigenic hormones)[57].

Summary

These studies indicate that hormones could mediate adaptation to heat by exerting central or peripheral effects to suppress thermogenesis, or might act peripherally to increase cutaneous heat dissipation or decrease the renal excretion of water and electrolytes (Fig. 1). However, many of these studies were performed in non-human animal models, and the influence of hormones on human thermoregulation remains to be elucidated.

Effects in key stages of the life course

Hormones have essential roles in key life stages, such as in childhood during growth, and in puberty, reproduction and pregnancy, lactation and the menopause. Here, we summarize evidence for the potential effects of heat exposure on the endocrine regulation of these processes.

In utero, childhood and puberty

Early life exposure to high temperatures might have adverse effects on child health[58]. However, whether heat exposure affects endocrine axis development in utero or postnatally in humans is unclear. Limited data from rodents indicate that intrauterine heat exposure could affect fetal endocrine development. Pregnant rats exposed to a temperature of 43 °C for 15 min had pups with brain malformations in association with decreased adrenal size and reduced numbers of pituitary somatotroph cells[59]. Moreover, prepubertal rats acutely exposed to heat had pituitary and adrenal degeneration, with decreased serum concentrations of corticosterone[60].

Pubertal timing in girls and boys is progressively occurring earlier due to multiple putative causes, including metabolic disorders such as obesity and environmental exposures such as endocrine-disrupting chemicals[61–63]. However, whether heat exposure influences the onset of puberty is unknown. The timing of puberty onset is regulated by hypothalamic kisspeptin-expressing neurons that activate gonadotropin-releasing hormone (GnRH) neurons[61,64]. In pigs, persistently increased ambient temperatures during the summer were associated with decreased hypothalamic kisspeptin expression, with reduced serum concentrations of GnRH, luteinizing hormone and follicle-stimulating hormone[65]. These findings highlight a potential mechanism by which heat could influence pubertal onset via effects on hypothalamic kisspeptin.

Reproduction, pregnancy and birth outcomes

The hypothalamic–pituitary–gonadal axis regulates cyclical changes of the female reproductive tract, including ovulation and endometrial development for embryo implantation[66]. Heat affects the rodent reproductive cycle, which lasts 4–5 days and is associated with endometrial resorption in the absence of fertilization[67]. Female rats repeatedly exposed to a temperature of 38 °C had decreased serum concentrations of oestradiol and progesterone and a longer dioestrus (luteal phase) than female rats kept at ~22 °C[68]. However, whether heat exposure affects the human menstrual cycle, which lasts around 28 days and is associated with endometrial shedding, is unclear[67]. A retrospective study involving >300,000 women showed no substantial effect of ambient temperature on menstrual cycle length[69]. Moreover, menstrual cycle phase seems not to affect heat tolerance: a direct calorimetry study involving healthy women undertaking exercise showed no effect of the menstrual cycle phase on heat production or loss[70].

In bulls and rats, heat exposure transiently decreases plasma concentrations of testosterone and spermatogenesis and in men, heat exposure impairs fertility[71–73]. However, the evidence is less clear for effects on fertility in women. A prospective study in women evaluated for infertility showed that exposure to increased ambient temperatures in the 90 days preceding a pelvic ultrasound scan was associated with a decreased antral follicular count, an indicator of ovarian reserve[74]. This observation might have been due to the effects of heat on ovarian follicular cells. Indeed, cultured ovarian follicles from dairy cattle exposed to a temperature of 41 °C for 48 h showed decreased steroid hormone synthesis and premature luteinization of follicular cells, which is associated with reduced fertility[75].

Pregnancy affects maternal thermoregulation, and pregnant women persistently exposed to increased temperatures might have an increased risk of maternal complications, such as gestational diabetes

mellitus[76,77]. Epidemiological evidence indicates that heat exposure during pregnancy increases the risk of adverse birth outcomes, such as preterm birth, stillbirth and low birthweight[77]. Whether pregnancy hormones influence these adverse outcomes is unknown. However, exposure to a temperature of 40 °C for 7 days during early pregnancy in mice caused autophagy of steroidogenic cells within the corpus luteum, which was associated with decreased serum concentrations of progesterone and impaired embryo implantation[78].

Lactation

Lactation is regulated by prolactin and oxytocin, which promote milk synthesis and let-down, respectively[34]. Human data are lacking on how heat affects lactation, although the time spent breastfeeding can decrease during periods of high ambient temperature[79]. By contrast, decreased milk yield is the most recognized consequence of heat exposure in dairy cows, and occurs despite heat causing a paradoxical increase in circulating concentrations of prolactin[80,81]. Heat-related decreased milk yield in livestock has multiple causes, including reduced food intake and direct effects of heat on mammary cells, which alter the expression of genes involved in prolactin and oestrogen signalling, and impair metabolic processes mediating milk synthesis[81,82]. Moreover, in hypothalamic, pituitary and mammary gland tissues from heat-stressed cows, the expression of long non-coding RNAs regulating target genes involved in pituitary secretion of thyroid hormone and GH, and mammary oxytocin and prolactin signalling pathways, was altered[83].

Menopause

Menopause is characterized by neuronal and hormonal changes (including oestrogen deficiency) that impair thermoregulation mediated by the POA[84], leading to increased heat dissipation manifesting as hot flushes that affect around 80% of postmenopausal women[84,85]. However, whether changes in ambient temperature exacerbate menopausal symptoms is unclear. Although one study found no association between hot flushes and season or temperature[86], further investigation of the effects of rising temperature on menopausal symptoms is warranted. In addition, whether menopause-related thermodysregulation increase the risk of heat injury remains to be determined.

Summary

A small number of studies, mainly involving rats, have shown that heat exposure affects fetal and prepubertal pituitary and adrenal glands, alters the reproductive cycle and might reduce fertility. Heat is also known to impair lactation in cows, perhaps in part due to effects on mammary hormone signalling. The effect of heat on puberty and the menopause is unknown.

Effects of heat on endocrine diseases

Global temperatures are rising as the number of people with endocrine diseases, particularly diabetes mellitus, is increasing. Furthermore, some endocrine diseases have the potential to cause maladaptive thermoregulatory responses and increase the risk of heat injury by impairing heat dissipation due to either sweat gland dysfunction or reduced cutaneous blood flow, or by causing increased renal water excretion and dehydration. These issues are discussed in the next sections.

Diabetes mellitus

Diabetes mellitus affects around 530 million people worldwide, with type 2 diabetes mellitus (T2DM) accounting for 96% of all cases[87]. The prevalence of T2DM is expected to increase as a consequence of obesity and demographic shifts, with around 1.3 billion people predicted to be affected by 2050 (ref. 87). A meta-regression analysis demonstrated an association with higher mean annual outdoor temperatures and increasing diabetes mellitus incidence in the USA and with the prevalence of glucose intolerance worldwide[52]. The prevalence of gestational diabetes mellitus might also be associated with increased temperature[76]. These epidemiological studies are supported by passive heating experiments involving human volunteers, which showed that acute exposure (≤4 h) to elevated ambient temperatures increases glucose intolerance in individuals with and without diabetes mellitus[88].

Diabetes mellitus is a risk factor for mortality and hospital admission related to heat exposure[89,90]. In a US study, patients with diabetes mellitus had a 17% higher risk of dying on hot days than those without diabetes mellitus and this effect was greater than that observed in those with other chronic diseases[91]. This increased risk of heat-related morbidity and mortality could involve a range of mechanisms. For example, patients with diabetes mellitus are susceptible to water loss and dehydration, which might increase the risk of hospitalization due to renal complications or a hyperosmolar hyperglycaemic state[90]. Diabetes mellitus is also associated with decreases in dermal blood flow and heat dissipation[92]. In men with T2DM, reduced sweat evaporation during exercise was associated with increases in body temperature and cardiovascular strain[93]. In addition, diabetes mellitus and heat exposure are both coronary artery disease risk factors, and so patients with diabetes mellitus exposed to heat extremes might potentially have an increased cardiovascular event burden.

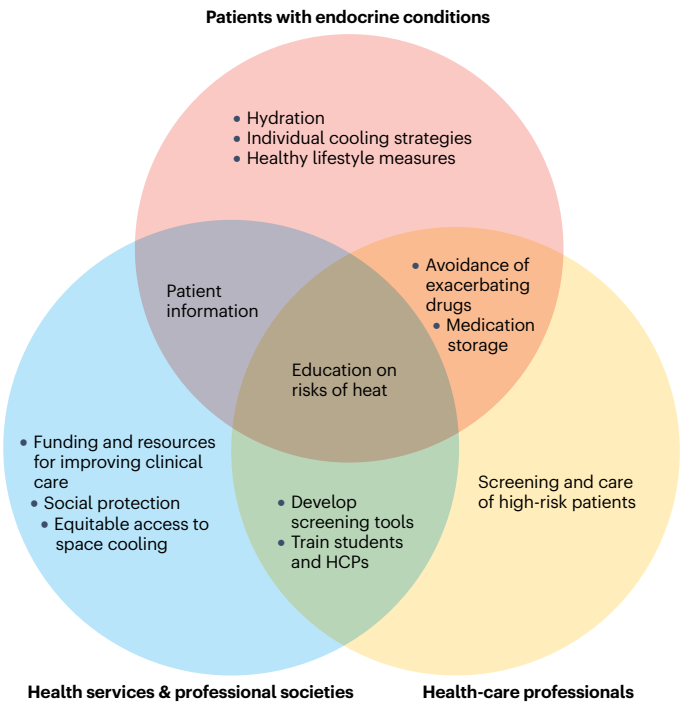
Patients with endocrine conditions
• Hydration
• Individual cooling strategies
• Healthy lifestyle measures
Patient information
• Avoidance of exacerbating drugs
• Medication storage
Education on risks of heat
• Funding and resources for improving clinical care
• Social protection
• Equitable access to space cooling
• Develop screening tools
• Train students and HCPs
Screening and care of high-risk patients
Health services & professional societies
Health-care professionals

Fig. 2 | Strategies for improving the care of patients with endocrine conditions who are at risk of heat injury and other health events. Patients, health-care professionals, and health services and professional societies are represented by red, yellow and blue circles, respectively. Non-overlapping regions show strategies relevant to individual groups and overlapping regions show strategies relevant to multiple groups. HCP, health-care professional. Adapted from ref. 5, Springer Nature Limited.

Table 2 | Drugs prescribed for the treatment of endocrine and metabolic conditions that might affect thermoregulation

Drug	Treatment indication	Mechanism of adverse thermoregulatory effects	Refs.
Drugs impairing sweating or heat dissipation			
SGLT2 inhibitors	T2DM	Polyuria-induced dehydration	8
Lithium	Thionamide-resistant hyperthyroidism		122
Loop diuretics	Hypercalcaemia; diabetes mellitus with heart failure		106
Metformin	T2DM	Diarrhoea-induced dehydration during treatment initiation phase	8
ACE inhibitors	Diabetic nephropathy	Impaired thirst and fluid intake causing dehydration	8
ARBs	Diabetes mellitus with hypertension		8
Oxybutynin	Diabetes mellitus with detrusor overactivity	Suppression of sweating	8,107,108
Topiramate	Metabolic syndrome and obesity	Suppression of sweating	123
Non-selective β-blockers (e.g. propranolol)	Hyperthyroidism	Impaired cutaneous vasodilation	8
Drugs increasing heat production			
Levothyroxine	Hypothyroidism	Increased metabolic rate	124
Liothyronine			125
Mirabegron	Diabetes mellitus with bladder overactivity	Increased brown adipose tissue metabolic activity	109
Testosterone	Hypogonadism	Increased heat stress susceptibility; potentially mediated by etiocholanolone, a testosterone metabolite with pyrogenic actions	126,127
Progesterone and progestogens	Assisted reproduction and gynaecological disorders	Pyrogenic action mediated by direct effects on the hypothalamus or via indirect effects on cytokine production	128

ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; SGLT2, sodium–glucose co-transporter 2; T2DM, type 2 diabetes mellitus.

Endocrine disorders with potential effects on thermoregulation

Thyroid disorders are associated with impaired thermoregulation. Although hyperthyroidism is characterized by heat intolerance, which could exacerbate heat injury, the consequences of heat exposure at the population level on thyroid disorders are largely unknown. In addition, clinical data are restricted to individual case reports. In one patient, heat stroke was the presenting feature of hypothyroidism[94]; in another, fatal heat stroke was associated with Hashimoto thyroiditis, a common cause of hypothyroidism[95]. These reports suggest that while hypothyroidism is typically characterized by cold intolerance, it might paradoxically predispose to heat injury by causing impaired sweating.

Adrenal insufficiency and hypocortisolaemia could also impair thermoregulation, as some patients with adrenal insufficiency have low or high body temperatures[96,97]. Rats with adrenal insufficiency have decreased resistance to temperatures in the range 37–40 °C and exhibit a higher colonic temperature when exposed to heat compared with healthy controls[98]. These findings suggest a decreased ability to dissipate heat[98].

GH deficiency might impair thermoregulation due to decreased sweating[99]. This possibility is supported by a study in young affected adults, who exercised in heat and developed hyperthermia in association with decreases in sweat secretion rate and sweat gland sensitivity to core temperature[99].

AVP deficiency is a disorder of water regulation associated with hypohydration and impaired heat dissipation[100]. This condition is reported to cause increased body temperature, and has been diagnosed in a patient with heat stroke[101,102].

Summary

Diabetes mellitus is a risk factor for heat-related morbidity and mortality. Case reports and small studies have indicated that thyroid disorders, adrenal insufficiency and deficiencies of GH or AVP, might also increase susceptibility to heat injury. Large-scale epidemiological studies are required to determine the effect of high environmental temperatures in patients with endocrine conditions.

Managing heat exposure in patients

Managing heat exposure in patients with chronic endocrine conditions requires the involvement of patients, physicians, health services, community health workers and social services, as well as professional organizations[5] (Fig. 2). Detailed assessment of patients with endocrine conditions enables clinicians to provide targeted advice on heat avoidance and personal cooling strategies. Screening tools can also be used in primary care to identify patients at high risk of heat injury, other health events or death. One reported tool incorporates quantitative environmental data (such as ambient temperature and humidity) and physiological measures (such as heart rate and core temperature) into a heat stress risk formula, and another tool employs a qualitative assessment of environmental, physical and social risk factors[103,104]. These screening tools require careful evaluation and have limited use without social information (for example, housing quality) that is a major determinant of heat-related mortality.

Patients should be encouraged to take individual measures during hot weather such as maintaining adequate fluid intake, consuming cold drinks, using cooling vests and incorporating periods of rest in cooled environments. Hydration is essential, as water deficits impair

thermoregulation and are associated with increased core temperature, particularly during physical exertion[105]. Adopting healthy lifestyle measures (such as regular aerobic exercise) will improve cardiovascular fitness and help acclimatization to increased temperatures[105].

Physicians should be aware that drugs affecting endocrine systems or used to treat diabetes mellitus might affect thermoregulation and exacerbate heat injury and heat-related health events. For example, in one study involving patients aged ≥65 years with chronic conditions, treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers or loop diuretics, which have the potential to cause dehydration (Table 2), increased the risk of heat-related hospitalization[106]. In addition, oxybutynin (used to treat diabetic overactive bladder and might also suppress sweating) has caused heat stroke in older patients[107,108]. Other drugs that might affect thermoregulation include: exogenous T_4 and T_3; β3-adrenergic receptor agonists that might increase metabolic heat generation; non-selective β-blockers (such as propranolol) that might impair cutaneous vasodilation and the capacity for heat dissipation; and sodium–glucose co-transporter 2 inhibitors (used to treat T2DM) that might cause polyuria and dehydration[8,109] (Table 2).

Injectable hormone replacement therapies ranging from insulin to parathyroid hormone are used to manage endocrine conditions. These biologics are sensitive to temperature extremes, and physicians should educate patients about the effect of heat on peptide stability and absorption, and provide guidance on the correct storage of medications during hot weather[5]. Pharmacies and other health facilities should store drugs in a cool environment and monitor the temperature of refrigerators containing drug stocks.

Improving education on the risks of heat

Health services and professional organizations such as endocrine societies can support physicians and patients by developing educational programmes and patient-based information on the risks of heat (Fig. 2). In particular, increased awareness is required about endocrine conditions such as diabetes mellitus, hypothyroidism and hyperthyroidism, and adrenal insufficiency impairing thermoregulation and potentially increasing susceptibility to heat injury. Heat exposure is an environmental and occupational health hazard that should be included in medical school curricula, and training should be provided to clinical trainees, nursing staff and endocrinologists on how to integrate heat prevention and mitigation measures into the clinical care of high-risk patients with endocrine conditions[5,105]. Endocrine societies and physician organizations also have a part to play in advocating for policies to tackle global warming, such as promoting energy efficiency and shifting energy production from fossil fuels to renewable sources.

The need for further research

Whether increased heat exposure occurring as a consequence of climate change has adverse effects on endocrine health is currently unclear. Epidemiological data for patients with endocrine conditions living in hot climates are lacking, and the effect of age, sex, pregnancy, comorbidities and medications on heat-related clinical outcomes in these patients is unknown. Multidisciplinary research involving the endocrine and global health research communities is required to evaluate the effects of rising temperatures and heatwaves on patients with endocrine conditions. Moreover, efforts should be focused on populations living in low-income and middle-income countries with limited

Box 1 | Recommendations for research relating to the endocrine effects of heat

Basic science research

- In vitro studies are required to assess how heat influences:
  - Hormone expression and secretion in endocrine cells and tissues.
  - Hormone receptor expression, activation, recycling, signalling and biological actions in target cells and tissues.
- Utilization of in vivo models to investigate:
  - The range of hormones influencing central and peripheral thermoregulatory processes.
  - The effects of chronic heat exposure on fetal and postnatal endocrine axis development.
  - The epigenetic and transgenerational endocrine effects of heat exposure.
  - How heat affects the pharmacokinetics and pharmacodynamics of exogenously administered hormones and other endocrine-targeted drugs.
  - The effects of heat on morbidity and mortality in models of endocrine disorders, such as hypothyroidism and adrenal insufficiency.
  - Strategies such as heat acclimatization for minimizing adverse health outcomes.

Clinical and epidemiological research

- Conduct passive heating and exercise heat stress studies to characterize how endocrine axes change in response to acute heat exposure.
- Use retrospective data or establish prospective cohorts in countries or populations that are most exposed to high temperatures for the following research:
  - Examine effects of high temperatures and extreme heat events on hormonal changes at key stages of the life course, such as infancy, puberty, pregnancy, lactation and menopause.
  - Identify how individual characteristics, such as age, sex and genetic polymorphisms, might affect endocrine adaptations to heat.
  - Improve the description of heat exposures (thresholds, magnitude and duration and timing of exposures) mediating adverse endocrine effects.
  - Assess clinical outcomes in patients with endocrine disorders with a focus on vulnerable groups, such as children, pregnant women, older adults and different types of workers with high heat exposures.
  - Characterize behavioural responses to heat in patients with endocrine disorders.
- Investigate the effects of drugs on thermoregulation.
- Evaluate heat risk screening tools for use with patients who have endocrine conditions.
- Develop and evaluate low-cost interventions and practical heat management strategies to prevent adverse endocrine effects of heat.

access to space cooling technologies, as these countries will have the greatest health burden associated with heat exposure. Research efforts should also prioritize establishing heat thresholds for adverse endocrine effects and developing low-cost interventions to facilitate heat acclimatization and prevent heat injury and other heat-related health events in patients with endocrine conditions (Box 1).

A combination of basic science and clinical research is also required to assess the effects of acute and chronic heat exposure on hormone secretion and action, and determine whether hormonal changes occur as a direct consequence of heat exposure or arise secondary to pathophysiological changes, such as hypovolaemia or cardiovascular strain (Box 1). Endocrine adaptation to heat has been incompletely characterized and data are lacking for a range of endocrine axes, such as parathyroid–kidney–bone. Furthermore, there is a paucity of research involving humans, with the available studies being largely historical and focused on acute heat exposure in healthy male volunteers, military recruits and athletes[105]. Such studies can provide insights into endocrine adaptation to acute heatwaves, but have limited applicability to long-term increases in environmental temperature caused by climate change. Moreover, despite substantial insights into thermoregulation generated from non-human animal models, limitations exist for translating findings from these models to the human setting. This lack of translatability is particular apparent for small mammals such as mice, which have a greater surface area to volume ratio, higher basal metabolic rate and a higher thermoneutral zone of around 30 °C compared with 20–22 °C for clothed humans[110,111]. In addition, differences exist between humans and other large mammals. For example, heat generation from microbial fermentation of feed contributes to thermoregulation in cows, whereas pigs lack functional sweat glands and instead dissipate heat through respiration and changes in body posture[112,113].

The influence of genetics and epigenetics on endocrine adaptation to extreme heat remains to be elucidated. Whole-genome and epigenome profiling of populations acclimatized to hot climates might yield insights into genetic variants and epigenetic alterations that protect against heat injury.

Climate change is also causing increased levels of humidity, worsening air pollution, and increased environmental chemical contamination, and is affecting the quality and quantity of water supplies[2,58]. These hazards can exacerbate heat-related health outcomes[2], and should be considered when developing studies to assess the effect of rising temperatures on patients with endocrine conditions.

Conclusions

Climate change will probably accelerate without considerable action on decarbonization, leading to increased heat exposure in the coming decades[1]. An increased understanding of the short-term and long-term effects of heat on endocrine health is required, so that effective interventions can be developed for patients most at risk from rising environmental temperatures.

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Author contributions

F.M.H., M.K.S.L., J.K.W.L., S.K. and T.E. researched data for the article and wrote the manuscript. S.H.K. and R.V.T. reviewed and edited the manuscript. All authors made substantial contributions to discussion of the content.

Competing interests

The authors declare no competing interests.

Additional information

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